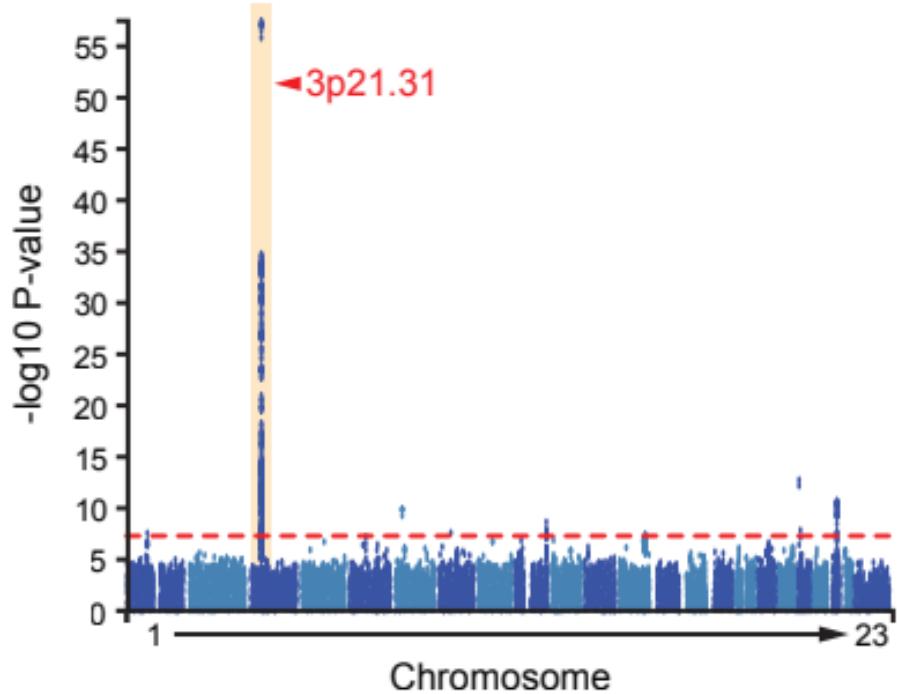


a

GWAS: Hospitalized COVID-19 vs. population

**b**

GWAS: Hospitalized vs. non-hospitalized COVID-19

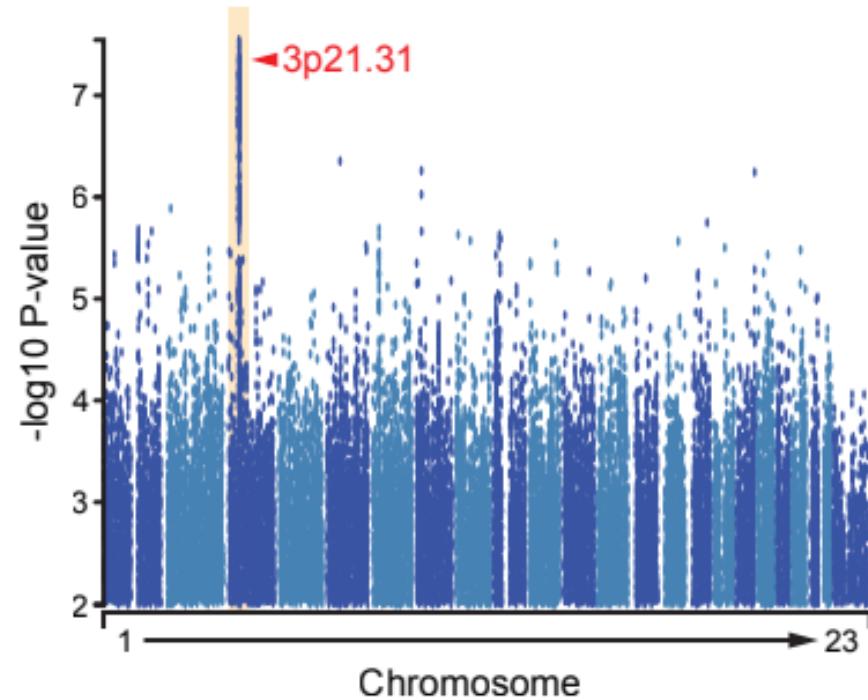
**Figure S1**

Figure S1. Overview of genome-wide genetic associations with severe COVID-19.

(a,b) Manhattan plots showing the strong association of the 3p21.31 locus with hospitalized COVID-19 (based on v4 GWAS meta-analysis release). Panel a compares hospitalized COVID-19 patients with healthy control subjects; panel b compares hospitalized with non-hospitalized patients.

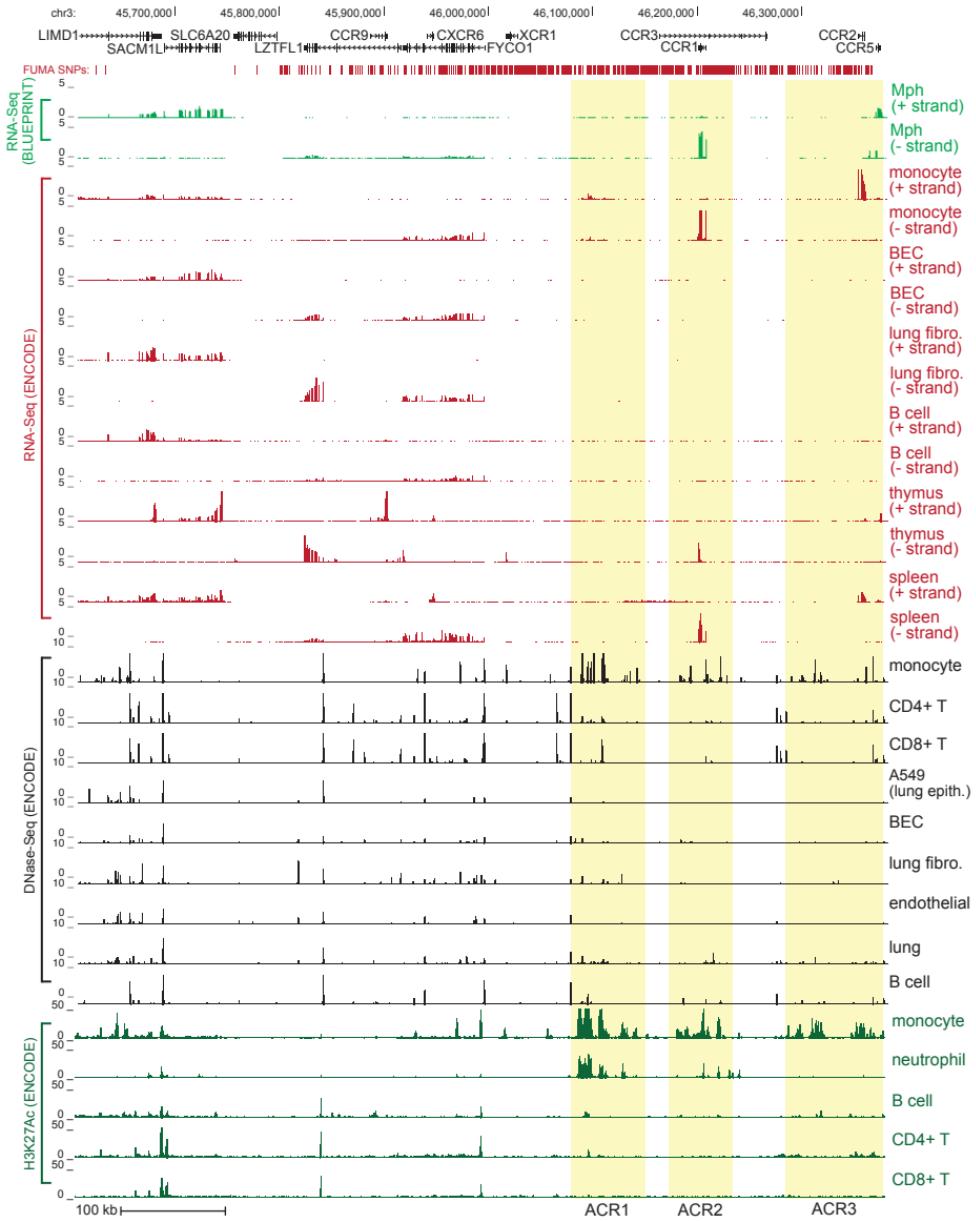


Figure S2

Figure S2. Transcriptional and epigenomic activity at 3p21.31 in selected cell types.
UCSC genome browser overview of RNA-Seq, DNase-Seq and H3K27Ac ChIP-Seq tracks for the indicated cell or tissue types (BEC: bronchial epithelial cell, fibro.: fibroblast, epith.: epithelial). Yellow shading indicates location of monocyte/macrophage-specific active chromatin regions ('ACR1-3').

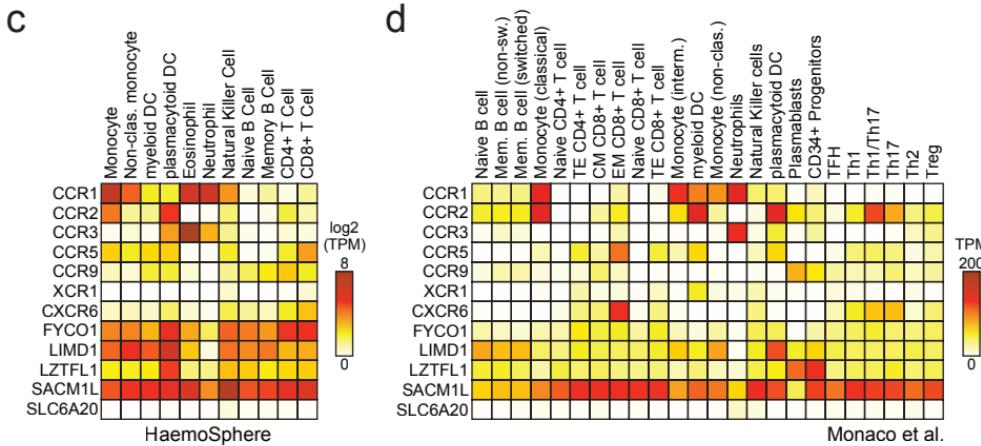
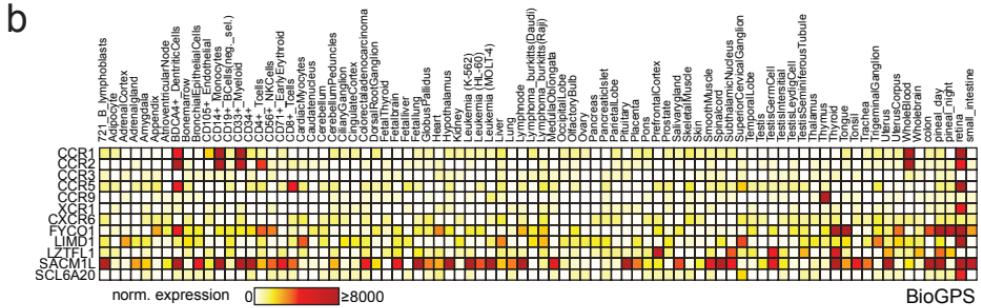
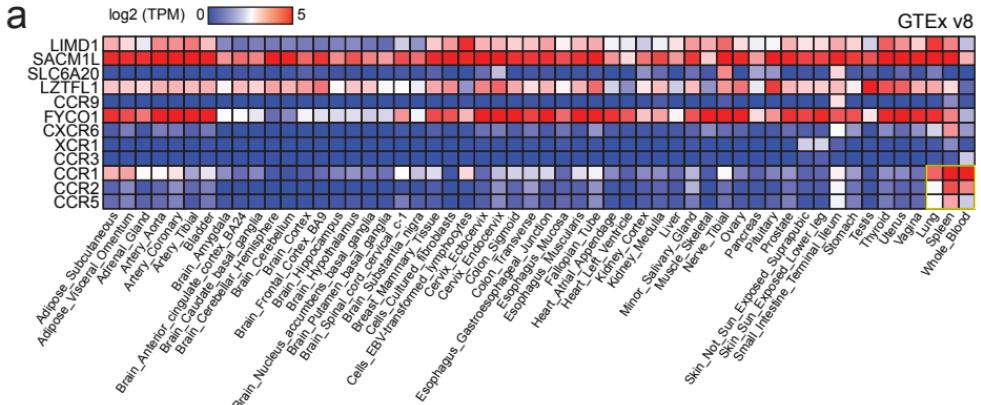
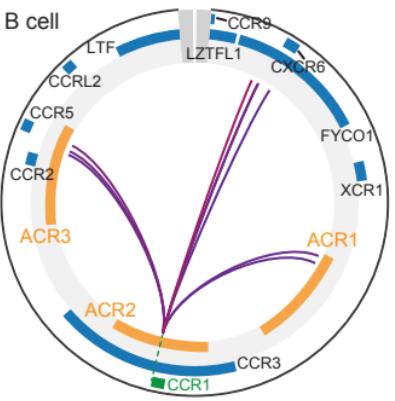
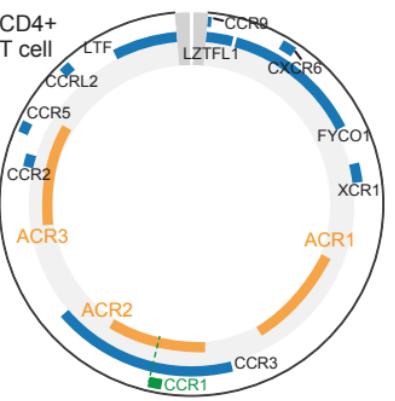
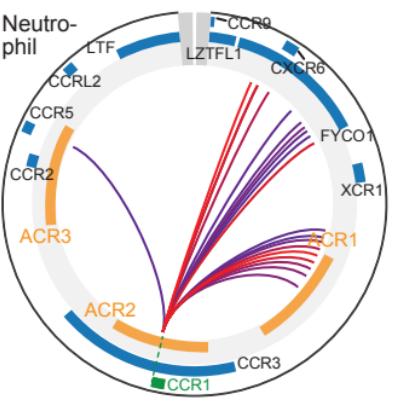
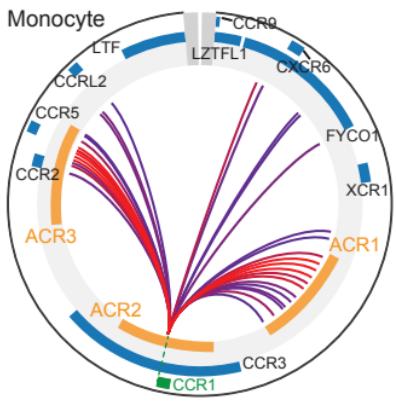


Figure S3

Figure S3. Gene expression analysis of 3p21.31 candidate genes across various non-immune and immune cells types. (a) Normalized gene expression levels (transcripts per million; TPM) across 54 tissues (GTEx v8 database). (b) Normalized gene expression levels (microarray-derived) across 84 tissues and cell types (BioGPS database). (c) Normalized gene expression levels (TPM) across 11 immune cell types (HaemoSphere). (d) Normalized gene expression levels (TPM) across 24 immune cell types (Monaco et al.[37]).

a

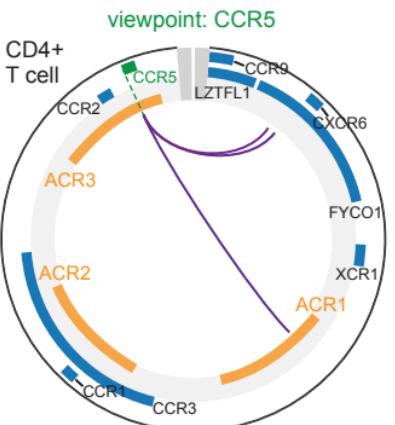
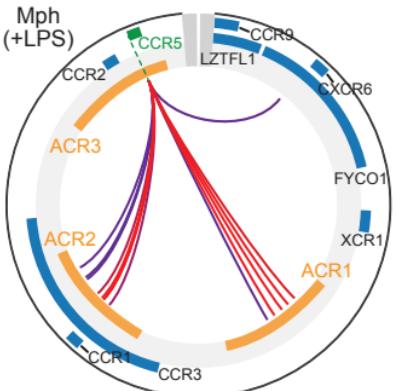
viewpoint: CCR1



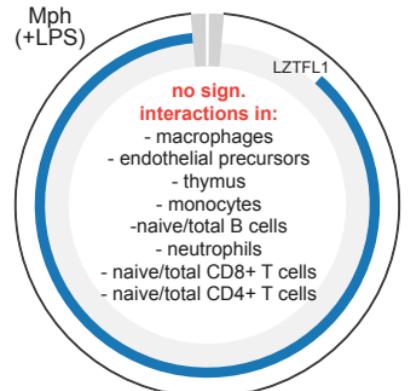
50
interaction freq.
7

b

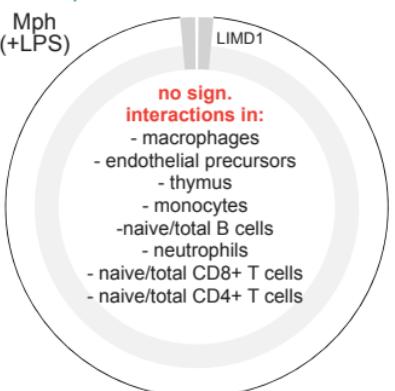
viewpoint: CCR5

**c**

viewpoint: lead SNP



viewpoint: most distal LIMD1 SNP



50
interaction freq.
7

Figure S4

Figure S4. Regulatory chromatin interactions across the 3p21.31 COVID-19 risk locus. (a) Circos plots showing significant chromatin interactions with the CCR1 promoter (green dashed line) in monocytes, neutrophils, CD4+ T cells and total B cells measured by promoter-capture Hi-C[14] (freq.: frequency). ACRs are indicated in orange. (b) Significant chromatin interactions with the CCR5 promoter (green dashed line) in LPS stimulated macrophages (Mph+LPS) or CD4+ T cells. (c) Lack of chromatin interactions emanating from the location of the lead GWAS SNP (left circos plot) or most distal SNP in the LIMD1 gene (right circos plot). Data shown is for LPS stimulated macrophages (Mph+LPS, but identical results were obtained for the indicated cell types.

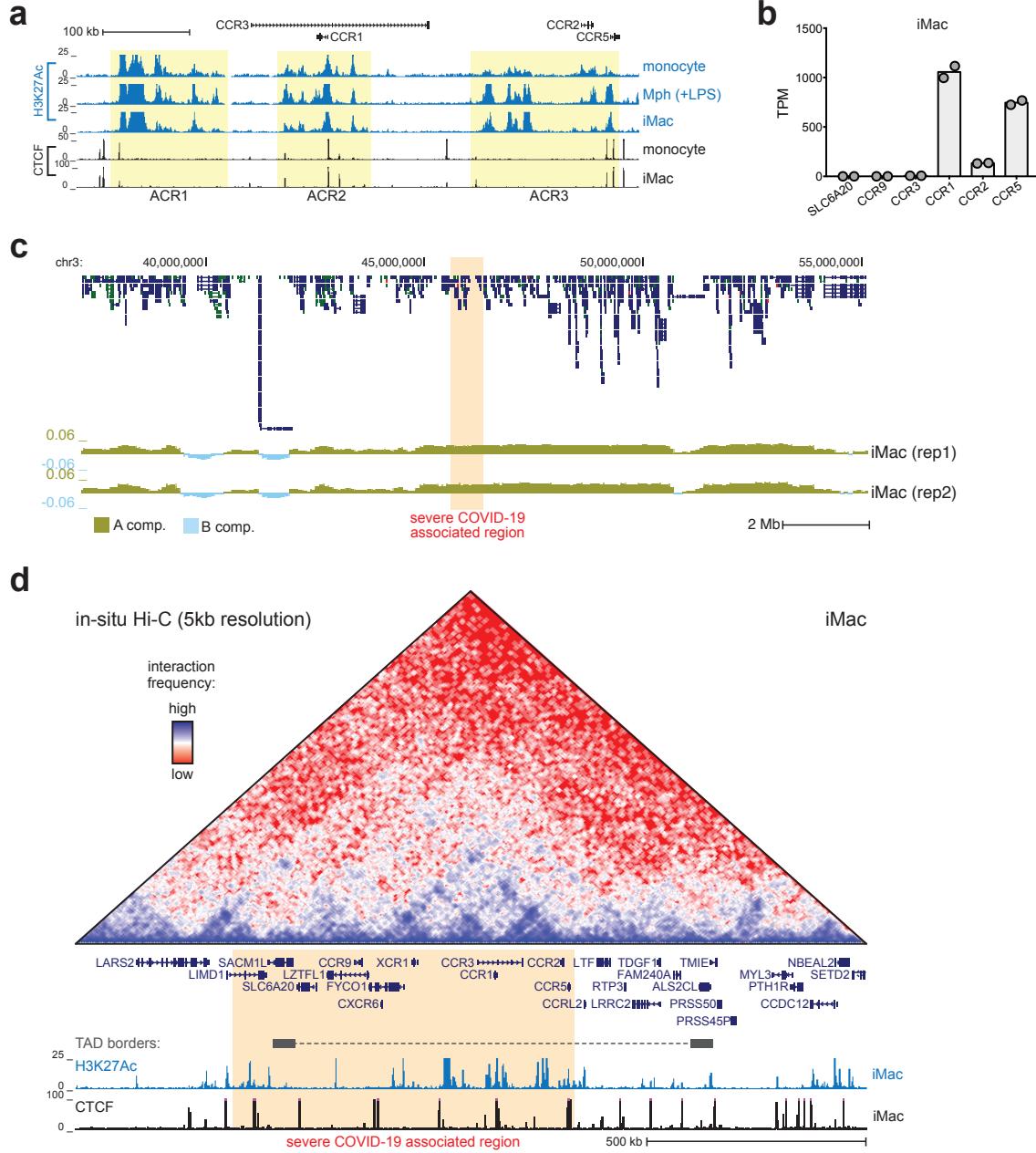


Figure S5

Figure S5. Epigenomic landscape and 3D genome folding at the 3p21.31 COVID-19 risk locus in iMacs. (a) UCSC genome browser view of H3K27Ac and CTCF ChIP-Seq signal for the indicated cell types. Yellow shading indicates location of monocyte/macrophage-specific active chromatin regions ('ACR1-3'). (b) Normalized gene expression levels (transcripts per million; TPM) for indicated 3p21.31 genes in iMacs. (c) Overview of A/B compartmentalization (derived from in-situ Hi-C) surrounding the 3p21.31 severe COVID-19 associated region (indicated by orange shading) in iMacs. PC1 values (at 100kb bin size) are shown as continuous profiles, with positive values (A compartment) in green and negative values (B compartment) in blue. (d) In-situ Hi-C contact map (at 5kb bin size) of the 3p21.31 COVID-19 risk locus in iMacs. TAD borders called are depicted as gray rectangles (called at 50kb resolution) and the topologically associating domain (TAD) encompassing most of the severe COVID-19 associated region (indicated by orange shading) is depicted by a dashed line. H3K27Ac and CTCF enrichment in iMacs is shown below.

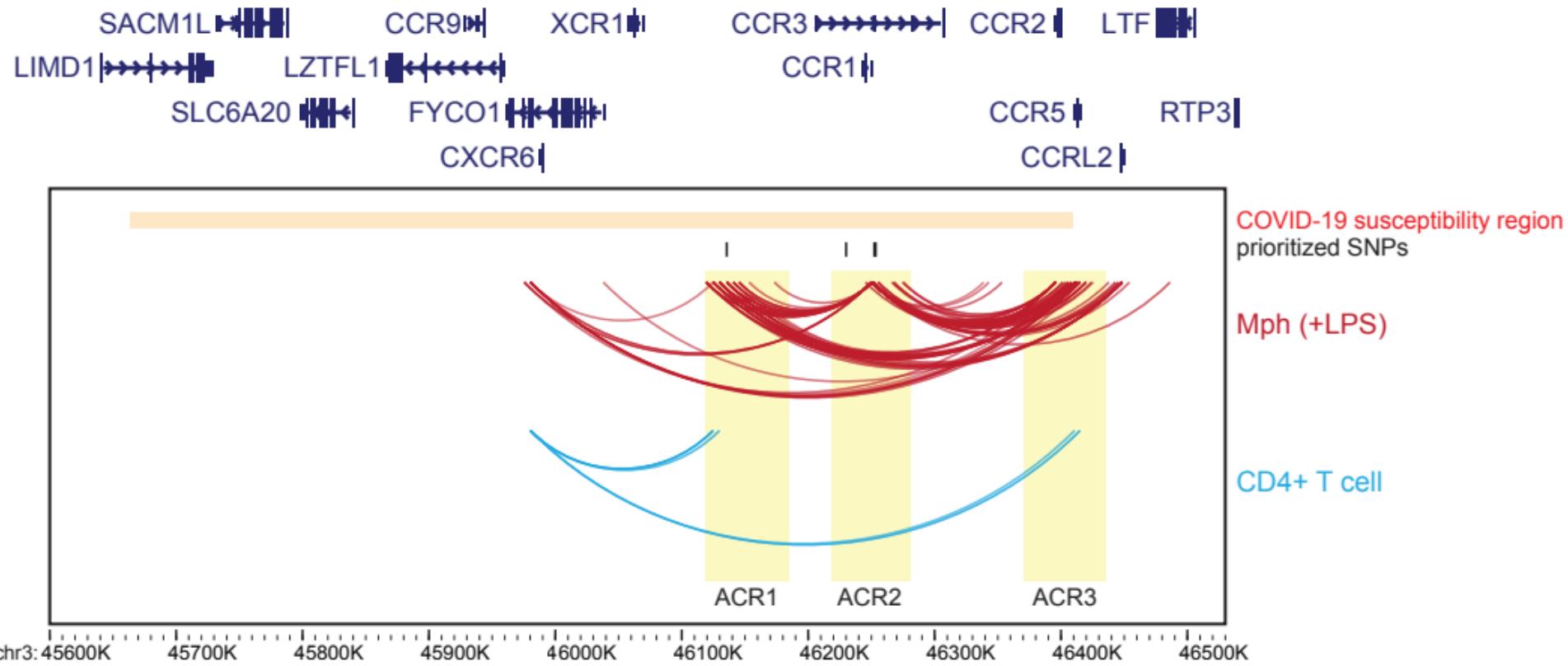


Figure S6

Figure S6. Chromatin interactions with prioritized 3p21.31 COVID-19 risk variants.

Promoter capture Hi-C (PCHi-C) interactions[14] detected in monocyte-derived macrophages stimulated with LPS (red arcs) and CD4+ T cells (blue arcs). Active chromatin regions (ACR) 1, 2 and 3, as well as the GWAS-defined COVID-19 susceptibility region are indicated by yellow and orange shading, respectively. Interactions were only shown if at least one anchor connected to an ACR but irrespective of interaction span. Interactions connecting an ACR with sequences outside the depicted region were not detected. The 4 prioritized SNPs (located in ACR1 and ACR2) are shown on top.

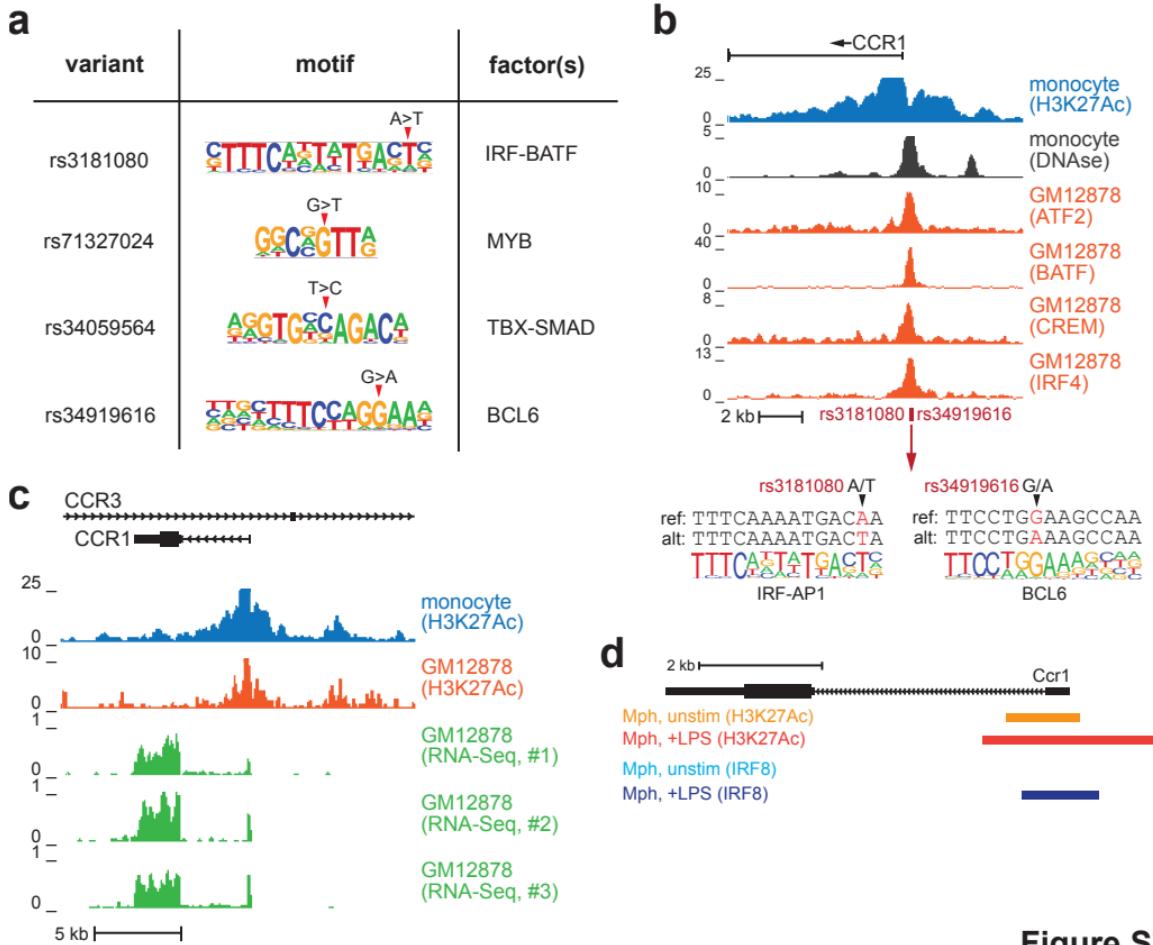


Figure S7

Figure S7. 3p21.31 COVID-19 risk variants disrupt putative transcription factor binding sites. (a) Transcription factor binding motifs overlapping with four candidate causal SNPs (see Fig.2e). Single nucleotide substitutions are indicated above the motif logos. (b) Zoom-in view of the CCR1 promoter (top) showing H3K27Ac, chromatin accessibility (DNase-Seq) and binding of AP1 (i.e. ATF2, BATF, CREM) or IRF4 transcription factors in the indicated cells (ENCODE database) overlapping two candidate causal SNPs. Binding motifs modified by the variants are indicated (bottom). Rs3181080 optimizes an IRF-AP1 composite motif (A>T), while rs34919616 disrupts a BCL6 motif (G>A). (c) UCSC genome browser view of the CCR1 gene (located inside an intron of CCR3) showing H3K27Ac ChIP-Seq and RNA-Seq data tracks for monocytes and GM12878 lymphoblastoid cells (ENCODE database). (d) UCSC genome browser view of the mouse Ccr1 gene. Locations of ChIP-Seq peaks for H3K27Ac and IRF8 detected in unstimulated or lipopolysaccharide (LPS) stimulated bone marrow-derived macrophages[24] are indicated by coloured rectangles.